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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,880	07/10/2003	Benjamin David Silverman	YOR920030162US1	2640
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RYAN, MASON & LEWIS, LLP 1300 POST ROAD SUITE 205 FAIRFIELD, CT 06824			EXAMINER NEGIN, RUSSELL SCOTT	
			ART UNIT 1631	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/616,880	Applicant(s) SILVERMAN, BENJAMIN DAVID	
	Examiner Russell S. Negin	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A. SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 June 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7-15 and 17-21 is/are pending in the application.
- 4a) Of the above claim(s) 10-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-9, 14, 15 and 17-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 August 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 27 June 2007 are acknowledged and the amendments are entered.

Claims 1-5, 7-15, and 17-21 are pending, and claims 1-5, 7-9, 14-15, and 17-21 are examined in this Office action.

Drawings

The amended drawings filed on 18 August 2004 are objected to because they are not labeled as "New Sheets" or "Replacement Sheets." Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If

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the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

The following 35 U.S.C. 101 Rejections are reiterated from the Office action of 29 March

2007:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 7-9, 14-15, and 17-21 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The following analysis of facts of this particular patent application follows the analysis suggested in the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility". Note that the text of the Guidelines is italicized.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- The claimed invention "transforms" an article or physical object to a different state or thing.
- The claimed invention otherwise produces a useful, concrete and tangible result.

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In the instant case, the claimed invention does not "transform" an article or physical object to a different state or thing because it is a method for calculating a global hydrophobic moment of a tertiary protein structure. This does not preclude the subject matter to be patentable as, for eligibility analysis, as

physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that produces a useful, tangible and concrete result. In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is "useful, tangible and concrete." The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory. (Guidelines, p. 20)

The question is thus whether the final result achieved by the claimed invention satisfies all three criteria of being useful, and concrete, and tangible.

Furthermore, the useful, tangible, and concrete result must be recited in the claim itself, rather than addressed in specification.

(2) **"TANGIBLE RESULT"** The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. The opposite meaning of "tangible" is "abstract."

The instant claims are drawn to a method for calculating a global hydrophobic moment of a tertiary protein structure. However, as claimed, the method does not

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produce a tangible result. For example, the method as claimed may take place entirely within the confines of a computer or a human mind without any communication to the outside world and without using or making available for use, the results of the computation. In an embodiment of the instant set of claims, the "outputting" step may cause the result to be presented to a user in the form of a carrier wave, which, per se, is not statutory. Thus, the instant methods of the claims do not produce any tangible result. This aspect of the rejection may be overcome by indicating the form by which the output is given to the user (i.e. on a display or on a computer readable medium).

There is an additional problem in the instant set of claims is "outputting the characterization of the amphiphilicity." It is not comprehended as to how a "characterization" of an "amphiphilicity" is a tangible quantity, result, or "thing" that is capable of being output.

Therefore, the final result achieved by the claimed invention does not satisfy all three criteria of being useful, and concrete, and tangible.

Response to Arguments:

Applicant's arguments filed 27 June 2007 have been fully considered but they are not persuasive.

Applicant's arguments on page 7 of the Remarks of 27 June 2007 rely on amendments to the instant independent claims that do not cause the claims to be statutory (see above 35 U.S.C. 101 rejection).

Claim Rejections - 35 USC § 112

The following rejection is necessitated by amendment of applicant filed on 27 June

2007:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-9, 14-15, and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the final steps of claim 1, 14, and 21, there is a step of outputting a characterization. Since a characterization is not a "thing," it is unclear as to how it can be output. Consequently, the metes and bounds of "characterization" are unclear.

Claim Rejections - 35 USC § 103

The following 35 U.S.C. 103 Rejections are reiterated from the Office action of 29 March

2007:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

35 U.S.C. 103 Rejection #1:

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Silverman [PNAS; April 24, 2001; volume 98, pages 4996-5001] in view of Clarke et al. [PNAS, 1999, volume 96, pages 7232-7237].

Claim 1 is drawn to a method for calculating a global hydrophobic moment of a tertiary protein structure comprising a plurality of residues, the method comprising the steps of:

- calculating a centroid of residue centroids;
- using the centroid of residue centroids as a spatial origin of a global linear hydrophobic moment;
- enhancing correlation between residue centroid magnitude and residue solvent accessibility;
- defining a global linear hydrophobic moment, wherein each of the residue centroids contributes a magnitude and direction to the global hydrophobic moment;
- using the global linear hydrophobic moment to characterize an amphiphilicity of a tertiary protein structure; and
- outputting the characterization of the amphiphilicity of the tertiary protein structure to a user.

Claims 2-4 are dependent from claim 1 with the additional limitations that the correlation between the residue centroid magnitude and the residue solvent accessibility is enhanced by using a distance metric, an ellipsoidal metric, and a solvent accessibility metric, respectively.

Claim 5 is dependent from claim 1 with the additional limitation that the centroid of residue centroids represents a geometric center of the tertiary protein structure.

Claims 7-9 are dependent from claim 1 with the additional limitations that the global linear hydrophobic moment characterizes the magnitude of amphiphilicity, direction of amphiphilicity, and identification of functional regions in the tertiary protein structure, respectively.

The article of Silverman, "Hydrophobic moments of protein structures: Spatially profiling the distribution," describes how to calculate moments of tertiary protein structures.

In equation [12] on page 4997 of Silverman, r_i is the vector pointing to the centroid of residue i while r_c is the vector pointing to the centroid of the entire protein molecule (i.e. the geometric center of the protein).

In equation [13] on page 4998 of Silverman, a first order hydrophobic moment imbalance about the entire protein is written, accounting for hydrophobicity and solvent accessible surface area. Each centroid of every protein residue contributes to this global moment.

In equations [13] and [14] on page 4998 of Silverman, distance metrics, ellipsoidal metrics, and a solvent accessibility are all used to enhance the centroid magnitude.

The global linear hydrophobic moment characterizes the amphiphilicity, and the magnitude and direction of the amphiphilicity of the tertiary protein structure.

Figure 6 on page 5000 of Silverman shows how an arm of the protein can be identified as it falls outside the ellipse characterizing the hydrophobic moment of the protein.

While Silverman demonstrates his technique for a secondary structural component of a protein, Silverman does not show his method for entire proteins.

Clarke et al. shows an isolated single structural element (i.e. a single alpha-helical peptide) comprising an entire protein. The study of Clarke et al., entitled, "The alpha-helix folds on the millisecond time scale" illustrates in Figure 4 at the bottom of column 1 of page 7236 the folding of a single unfolded peptide into a single helix. Clarke et al. explains on page 7232 under "Materials and Methods" that the compositions of the proteins used to attain the single alpha-helix were polyglutamic acid and polylysine.

While Clarke et al. refers to the molecules in their study as "peptides," peptides are defined in page 16 of the "Glossary of Medical Terms" as "a protein with a small number of amino acids." Consequently, a peptide is a protein.

Even though such proteins as described in Clarke et al. are small, they do not lack structure (i.e. primary, secondary, or tertiary). The definition of "protein tertiary structure" is "the folding of a protein into a 3-D structure." A peptide consisting of an alpha helix is a protein with a three dimensional structure.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the secondary structural element of a protein in Silverman by use of an entire protein with a secondary structure that it equivalent to a

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tertiary structure as shown in Clarke et al. because while Silverman illustrates a method of moment calculation on a portion of a protein, Clarke et al. has the advantage of utilizing proteins comprised in their entireties of single structural units (i.e. the units analyzed by Silverman) for the purpose of better understanding the kinetics of folding of alpha-helices.

Response to Arguments:

Applicant's arguments filed 27 June 2007 have been fully considered but they are not persuasive.

Applicant first argues on pages 7-9 of the Remarks that the definition of tertiary structure has been misinterpreted from the literature. This argument is not found to be persuasive, because the definition of tertiary structure in the literature is broad and can encompass many different aspects of the protein structure. Below are examples of the term tertiary structure:

1. Lines 15-16 of page 9 of the Remarks of 27 June 2007 states that the small, single domain, peptides of Poly(Glu) and Poly(Lys) have no tertiary structure.
2. The recent study of Kaur et al. [Proteins & Peptide Letters, 2007, volume 14, pages 626-631] predicts the tertiary structure of small, bioactive, and single domain peptides.
3. The definition of "protein tertiary structure" on the Web [www.google.com] states the definition of protein tertiary structure is "the folding of a protein into a 3-D structure."

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4. The definition of "protein structure, tertiary" on the Web [cancerweb.ncl.ac.uk]

states:

The stage in the structural development of a protein in which combination of alpha helices and beta sheets pack together to form a compactly folded globular units names domains. Small protein consist of only one domain but larger proteins contain a number of domains which are usually connected by open lengths of polypeptide chain. This stage is a combination of the second and third folding levels of protein binding.

While examples 1 and 4 imply that single domain structures do not have tertiary structures, examples 2 and 3 state that small, single domain peptides do have tertiary structures.

Given the conflicting definitions in the literature, and the lack of a definition of "tertiary structure" in the specification, the meaning of "tertiary structure" is broadly interpreted to be any of the four definitions mentioned above.

Applicant next argues on pages 9-10 of the Remarks that the tertiary structures examined are "entire tertiary proteins structures." However, Clarke et al. claims that "after initiation the helix will propagate rapidly, forming a very long helix, including nearly all residues." This is not found to be persuasive because of the words "after initiation." Before initiation, a single domain helix exists with a three dimensional tertiary structure.

35 U.S.C. 103 Rejection #2:

Claims 14-15 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Silverman in view of Clarke et al. as applied to claims 1-5 and 7-9 above, in further view of Michaud [USPAT 4,017,721].

Claim 14 is drawn to an apparatus for calculating a global hydrophobic moment of a tertiary protein structure comprising a plurality of residues, the apparatus comprising:

--a memory; and

--at least one processor operative to:

--calculate a centroid of residue centroids;

--use the centroid of residue centroids as a spatial origin of a global linear hydrophobic moment;

--enhance correlation between residue centroid magnitude and residue solvent accessibility;

--define the global linear hydrophobic moment, wherein each of the residue centroids contributes a magnitude and direction to the global linear hydrophobic moment;

--use the global linear hydrophobic moment to characterize an amphiphilicity of the tertiary protein structure; and

--output the characterization of the amphiphilicity of the tertiary protein structure to a user.

Claim 15 is dependent from claim 14 with the additional limitation that the centroid of the residue centroids represented a geometric center of the tertiary protein structure.

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Claim 17 is dependent from claim 14 with the additional limitation that the global linear hydrophobic moment is used to identify functional regions of the tertiary protein structure.

Claims 18-20 are dependent from claim 14 with the additional limitation that the correlation between residue centroid magnitude and residue solvent accessibility is enhanced using a distance metric, ellipsoidal metric, and solvent accessibility metric, respectively.

Claim 21 is drawn to an article of manufacture for calculating a global hydrophobic moment of a tertiary proteins structure comprising a plurality of residues, comprising:

--a computer-readable medium having computer-readable code embodied thereon, the computer-readable code comprising:

--a step to calculate a centroid of residue centroids;

--a step to use the centroid of residue centroids as a spatial origin of a global hydrophobic moment;

--a step to enhance correlation between residue centroid magnitude and residue solvent accessibility;

--a step to define the global linear hydrophobic moment, wherein each of the residue centroids contributes a magnitude and direction to the global linear hydrophobic moment;

--a step to use the global linear hydrophobic moment to characterize an amphiphilicity of a tertiary protein structure; and

--a step to output the characterization of the amphiphilicity of the tertiary protein structure to a user.

Silverman in view of Clarke et al. as evidenced by "Glossary of Medical Terms" as evidenced by the definition of "protein tertiary structure" as applied to claims 1-5 and 7-9 above do not teach a computer apparatus of programmable media for performing the claimed analysis.

The patent of Michaud, entitled, "Method and apparatus for determining the position of a body," uses a digital analysis system to calculate a centroid of a body. It is inherent, that in this computer system, there is a computer programmable media to control the computer system.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify Silverman in view of Clarke et al. as evidenced by "Glossary of Medical Terms" as evidenced by the definition of "protein tertiary structure" as applied to claims 1-5 and 7-9 above in further view of Michaud because the invention of Michaud has the advantage of using a computerized system to calculate centroids of objects which provide a more efficient means of calculating physical aspects of objects (i.e. physical aspects of proteins) than calculation by hand.

Response to Arguments:

Applicant's arguments filed 27 June 2007 have been fully considered but they are not persuasive.

Applicants argue in pages 10-11 of the Remarks that the Michaud patent does not overcome the deficiencies of the references utilized in the 35 U.S.C. 103 Rejection #1. This is not found to be persuasive because the references cited in the first 35 U.S.C. 103 rejection are not deficient.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

 9/14/07

RSN

14 September 2007

/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.

PRIMARY EXAMINER